

Inventors:

Pascal DELRIEU
18, rue Camille Claudel
31320 Castanet Tolosan
French citizen

Li DING
3, rue Mouloudji
31320 Castanet Tolosan
French citizen

COSMETIC PARTICULATE GEL CARRIERS FOR TOPICALLY APPLIED
ACTIVE AGENTS

CROSS-REFERENCE TO RELATED APPLICATIONS

1 This application is a continuation of our copending U.S. patent application
2 number 09/431,742 filed November 1, 1999, now United States Patent No.
3 6,319,507. Application number 09/431,742 was a continuation-in-part of our
4 copending international patent application PCT/IB98/00977 filed 01 May 1998
5 which application claimed priority from our United States Patent Application
6 No. 08/850,167 filed May 2, 1997 now United States patent number 5,961,990.
7 The disclosures of the aforementioned United States patents and patent
8 applications and of the aforementioned international application, are hereby
9 incorporated herein by reference thereto. *The benefit of continuation status is not*
10 *being claimed at this time with regard to applications numbers PCT/IB98/00977 and*
11 *08/850,167. However, this statement is made without prejudice to applicant's right to*
12 *claim continuation status, with respect to another application, at any time during the*
13 *pendency of the present application.*

BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention relates to a novel cosmetic or dermatological delivery system having a variety of applications for delivery of topically applied active agents to the skin, to methods of preparing such delivery systems and to cosmetic or dermatological formulations in which the delivery systems may be incorporated. Of particular interest are multiphase cosmetic formulations such as gels, creams and lotions.

One difficulty with known cosmetic delivery systems is that of protecting labile compounds from reacting prematurely. Furthermore, certain biologically active substances, e.g. alpha hydroxy acids, are known to benefit the skin by improving skin softness and appearance. However, many such actives tend to cause irritation because they have the capacity, if the local concentration is too high, to penetrate deeply through the stratum corneum to more sensitive living tissue. Accordingly, there is a need for a delivery system that can separate active agents from a formulating excipient or adjuvant and provide controlled release of the active substances at the point of application. It would also be advantageous to provide a delivery system for actives that permits localized concentration of actives at the point of delivery, for instance, at the skin's surface.

One approach is for actives to be bound to carrier molecules to provide a complex which will remain stable in cosmetic preparations. When the complex is applied to the skin, the active is released or dissociated from the delivery system and is absorbed into the skin to provide the desired effect. Such systems are known to the art, but they fail adequately to separate the actives from formulation ingredients. Nor do they provide a means for concentrating delivery of actives at a desired location, for example the skin's surface. Another problem encountered in delivering actives to the skin is that they may react

1 undesirably with the delivery system itself. Cosmetic actives can be stabilized in
2 suspensions and formulas as cosmetic preparations. However, formulating the
3 thus stabilized actives requires elevated temperatures and varying pH levels
4 which may modify the active and cause stability problems with the formulation.
5

6 Polyphenols such as procyanidin oligomers, are good examples of labile actives
7 that are known to polymerize undesirably in reaction with common components
8 of many cosmetic formulations. Polyphenols include catechins which are
9 botanically derived antioxidant polyphenols extracted from grape seed, green tea
10 and other woody plants. Catechins are useful for free radical scavenging in anti-
11 ageing formulations to protect against the effects of ultraviolet light.
12

13 A multilayer particulate delivery systems for these and other active ingredients,
14 and for controlled systemic release of drugs, is taught by Samain *et al.* in the U.S.
15 Patent No. 5,151,264. Samain *et al.* disclose what they describe as "biomimetic"
16 carriers comprising an absorbent, solid, core of modified starch and an outer
17 phospholipid coating which mimics a typical cellular membrane to avoid
18 triggering the body's defenses to the incursion of foreign particles. Though
19 Samain *et al.*'s multi-layer particles are very effective for many applications, it
20 would be desirable to have a delivery system that provides additional options
21 for release of the active at the delivery point or zone, and which permits quicker
22 release at the skin's surface than is possible from Samain's dimensionally stable
23 solid core particles.
24

25 Delivery systems for active substances having biologic or cosmetic activity,
26 "actives" herein, can be either sustained release or controlled release systems.
27 Sustained release systems release the active continuously from the moment of
28 formulation. The active to be delivered is embedded within a matrix whose
29 diffusion coefficient is low (lower than water for instance) so that the active

1 slowly releases out of the matrix. This type of continuous release system is not
2 suitable for cosmetic formulations because constant release of the active upon
3 formulation of the system, for example into a cosmetic cream, creates instability
4 affecting shelf life and effectiveness. In contrast, controlled release systems
5 release the active when initiated by a particular event. The active is chemically
6 or physically bound to a matrix in the controlled release system and is
7 subsequently released when that bond is destroyed by an external event. For
8 example, with the Samain *et al.* multilayer particles, the active ingredient is
9 linked to the particle by means of ionic bonding. The release of the active is
10 initiated by encounter with skin moisture, which has a relatively low ionic
11 strength.

12
13 Gel forming polymers provide a delivery system by forming a matrix in which
14 active substances can be entrapped. An example of a gel forming polymer is
15 agar, also known as "agar-agar", a polysaccharide commonly used as a medium
16 for electrophoresis and chromatography. It is known that agar can be formed
17 into beads of various sizes for delivery of actives such as pharmaceutical drugs
18 or even biological cells. A problem with agar beads is that they form a sustained
19 release system which, as described above, is not suitable for cosmetic
20 applications because release of the actives commences at formulation.

21
22 **2. Description of Related Art Including Information Disclosed under 37**
23 **CFR 1.97 and 37 CFR 1.98**

24 Cini *et al* U.S. Patent No. 5,457,093 discloses a sustained release gel formulation
25 for delivering growth factors to wound sites, especially ophthalmic wounds.
26 Various polysaccharide gels are used, including agar. Cini's gels are not
27 intended for formulation into cosmetics and would presumably dissolve or
28 disperse and fail to protect their actives, if subjected to mixing with an aqueous
29 phase cosmetic vehicle. The actives are continuously released from the gel from

1 the moment the gel is incorporated into a cosmetic formulation containing an
2 aqueous phase. Accordingly, Cini's gel formulations cannot be used in cosmetic
3 emulsions that are required to have significant shelf lives.

4
5 Modi U.S. Patent No. 5,417,982 discloses a controlled release delivery system
6 where a polymer-gel matrix comprised of two-water-soluble polymers is
7 incorporated into microspheres. Biodegradation of the microsphere matrix
8 provides a controlled release oral or injection delivery system for administering
9 therapeutic doses of proteins or polypeptides internally or systemically. Modi's
10 system is apparently not intended for, and would not be suitable for, topical
11 delivery and release of actives.

12
13 Rencher U.S. Patent 5,314,915 provides a local anesthetic delivery system
14 comprising a polymer blend of sodium carboxymethyl cellulose and xanthan
15 gum or sodium alginate. Rencher's formulation is a continuous phase adhesive
16 or teething gel, rather than being particulate, and does not provide a delivery
17 system that will facilitate the incorporation of actives in a cosmetic or
18 pharmaceutical formulation with good separation of the active from the
19 formulation. Rencher's continuous phase system does not protect any adsorbed
20 actives if incorporated into a cosmetic cream or lotion containing an aqueous
21 phase.

22
23 Yarosh U.S. Patent 5,077,211 discloses delivery of DNA repair enzymes in active
24 form to living mammalian cells *in situ* by incorporating purified enzymes into
25 liposomes which are diluted into media and added to target cells. The DNA
26 enzymes are reportedly active topically and elsewhere to correct cellular
27 deficiencies, stimulating generation of healthy tissue to replace aged or damaged
28 skin. Yarosh's liposomes are prepared by rehydrating lipid mixture films with a
29 concentrated, buffered, aqueous solution of the enzyme, agitating, sonicating and

1 separating out the desired liposome spheres. Lipid mixtures used are based
2 upon phosphatidyl choline (lecithin) as a primary ingredient, with dicetyl
3 phosphate or stearylamine as secondary ingredients and with cholesterol an
4 optional tertiary ingredient, see Examples 3 and 4.

5
6 According to Yarosh, the liposomes are incorporated into polyglycol gels,
7 apparently at room temperature, for topical application, apparently under
8 laboratory conditions. Consideration of Yarosh's delivery vehicles suggests that
9 while they may be adequate for laboratory testing, they would not be suitable for
10 commercial applications.

11
12 Yarosh U. S. Patent No. 5,352,458 and Kripke *et al.* U.S. Patent No. 5,302,389
13 disclose the use of Yarosh's DNA repair enzymes, prepared according to Yarosh
14 '211, respectively for enhancing tanning by stimulating enhanced melanin
15 production, and for suppressing UV-induced T-cell immune response and thence
16 the associated redness, tenderness and inflammation.

17
18 Clearly, significant benefits might be obtained from a cosmetic or pharmaceutical
19 formulation having a carrier to deliver such DNA repair, or other enzymes, in
20 active form, for topical application to the skin by consumers with or without
21 professional supervision. The difficulty is that enzymes are labile and subject to
22 denaturing by formulation temperatures or pH conditions, or by reaction with
23 cosmetic vehicles during the extended periods of shelf storage that are normal in
24 the cosmetic and pharmaceuticals manufacturing and distribution chains.

25
26 Neither the liposomes described by Yarosh, nor the liposome gel would appear
27 to offer sufficient protection to permit Yarosh or other enzymes to be formulated
28 into consumer cosmetic products, such as creams, lotions or gels having
29 adequate stability. The elevated processing temperatures, dispersing agents and

1 extended shelf life required may decompose or denature not only the enzymes
2 but their liposome carriers leading to unacceptable separation, loss of activity
3 and the like.

4
5 There is accordingly a need for an esthetic cosmetic carrier for topically applied
6 active agents that can protect labile actives such as botanical extracts,
7 desquamating enzymes and the like, and deliver such agents to the skin in active
8 form, while being suitable for formulation into traditional cosmetic vehicles.

9 There are further needs for cosmetic or pharmaceutical delivery systems which
10 offer separation of active from formulation ingredients and which can maintain
11 that separation through typical formulation processes, especially those required
12 for providing emulsions and for delivery systems which provide controlled
13 release of actives at a delivery point and preferably also permit localized
14 concentration of actives at the delivery point.

15 16 SUMMARY OF THE INVENTION

17 The invention, as claimed, is intended to provide a remedy for the problem of
18 providing a delivery system for delivering labile and other actives to the skin, or
19 other body surface, for topical application in a cosmetic or pharmaceutical
20 formulation. It furthermore solves problems of delivering actives that may react
21 undesirably with the delivery system itself, damaging the active or causing
22 stability problems with the formulation.

23
24 Accordingly, the invention provides a protective cosmetic particulate gel
25 delivery system for a topically applied active agent comprising discrete gel
26 particles formed of:

- 27 a) an agar gel; and
28 b) a restraining polymer dispersed in the agar gel, the restraining polymer
29 having sufficient molecular weight to prevent egress of the restraining

1 polymer from the agar gel, having retention groups to bind the active
2 agent to the restraining polymer for retention in the gel particles and
3 being present in a proportion sufficient to deliver an effective amount of
4 the active agent;

5 wherein the gel particles are manually crushable on the skin to increase the
6 surface area of the gel particle material and expose the restraining polymer to the
7 skin or other body surface for release of the active agent.

8
9 Preferably, active agent molecules are bound to the restraining polymer retention
10 groups and the restraining polymer has an average molecular weight of at least
11 100,000 daltons. In a preferred embodiment, the active agent and the retention
12 groups both comprise polar groups and are of opposite polarity whereby the
13 active agent can bind ionically with the retention groups. A suitable restraining
14 polymer is water-soluble and has a polysaccharide backbone substituted with
15 strongly cationic quaternary ammonium groups which can act as retention
16 groups for a range of active agents. The cationic ammonium groups are able to
17 form stable ionic bonds with anionic actives which bonds can be broken to
18 release the active upon topical application of the containing cosmetic
19 composition.

20
21 Some suitable ionically bondable active agents are antioxidants, e.g. vitamin C
22 (ascorbic acid), botanically derived polyphenols, procyanidin oligomers, free
23 radical scavengers, and topically active enzymes. Desired nonionic actives, for
24 example vitamin E (alpha-tocopherol), can bind to lipid groups on preferred
25 restraining polymers, by hydrophobic interaction. While agar is a particularly
26 preferred gel-forming agent, other gel-forming agents that meet the
27 requirements of the invention can be used.

28
29 The invention thus provides a delivery system for delivering actives to the skin

1 wherein one or more active agents is entrapped within a complexed-agar bead
2 containing, in addition to agar, a restraining polymer to which the active bonds
3 and from which it is not released until it reaches a target environment. The agar
4 complex beads can be formed in various sizes to deliver actives, including
5 pharmaceutical drugs or even biological cells, to the skin and applied to the skin
6 as soft crushable beads.

7
8 Many desired active materials entrapped in an agar gel, leach out over time,
9 especially if stored in an aqueous vehicle. In contrast, the restraining polymer
10 has a molecular weight sufficient, for example 100,000 daltons or more, to
11 prevent it from being released out of the agar matrix, so that, being bound to the
12 polymer, the active is not released from the agar bead. The agar beads formed
13 are preferably soft enough to be crushed on the skin during normal application
14 of a cosmetic formulation.

15
16 The invention also provides a method of preparing agar gel particles comprising
17 the steps of:

- 18 a) dissolving agar in water heated to an elevated temperature sufficient to
19 dissolve the agar, in a proportion of agar to water effective to form a gel at
20 lower temperatures; and
21 b) mechanically dispersing the agar solution in a cold hydrophobic liquid
22 immiscible with the agar solution maintained at a temperature below the
23 agar gelling point;

24 with the improvement that a water-soluble restraining polymer is included in the
25 agar solution whereby the drops are formed into gel beads incorporating the
26 restraining polymer.

27
28 Preferably, though not necessarily, the hot agar solution to an intermediate
29 temperature above the gelling point of the agar solution prior to performing step

1 b). In a preferred embodiment, which is simple and economic to practice, the
2 agar-restraining polymer solution is mechanically dispersed in the cold
3 hydrophobic liquid by using a rotating agitator. Using this method, the gel bead
4 size can be controlled by selecting the rotation speed of the agitator.

5
6 In an alternative embodiment, the agar-restraining polymer solution is
7 mechanically dispersed in the cold hydrophobic liquid by injection through a
8 hollow needle to form drops, the needle having an internal dimension selected to
9 provide a desired gel bead size.

10
11 An advantage of employing a cooling step is that temperature-sensitive active
12 agents can be admixed with the cooled agar-restraining polymer solution, prior
13 to step b), avoiding the higher temperatures required for step a). Other active
14 agents can be admixed in step a). Either way, the active agent is effectively
15 incorporated in the gel beads, where it will be protected from possibly damaging
16 cosmetic, or pharmaceutical or other ingredients with which the beads may be
17 formulated, and is available to be topically delivered by crushing the beads on
18 the skin.

19
20 While reference is made herein to the skin as a delivery target for active agents, it
21 will be appreciated that the nails, hair, mouth, teeth wound tissue, or other
22 accessible endogenous body surfaces can be similarly targeted, depending upon
23 the active and the cosmetic or medicament vehicle into which the beads are
24 formulated.

25 26 BRIEF DESCRIPTION OF THE DRAWINGS

27 Some illustrative embodiments of the invention, and the best mode contemplated
28 of carrying out the invention, are described in detail below with reference to the
29 accompanying drawings in which:-

- 1 **Figure 1** is a schematic view of an embodiment of cosmetic gel particle
2 carrier according to the invention which takes the form of an agar
3 bead;
4 **Figure 2** is a schematic view showing several of the agar beads shown in
5 Figure 1 being crushed on the skin of a user;
6 **Figure 3** is a schematic representation of a prior art process for making agar
7 gel beads;
8 **Figure 4** is a block flow diagram of one method of manufacturing agar-
9 polymer complex beads according to the invention;
10 **Figure 5** is a block flow diagram of another method of manufacturing agar-
11 polymer complex beads according to the invention;
12 **Figure 6** is a schematic view of another method of making gel beads
13 according to the invention; and
14 **Figure 7** is a schematic view of apparatus for manufacturing gel beads by
15 the method illustrated in Figure 6.
16

17 DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

18 All parts and proportions referenced in this description, unless otherwise stated,
19 are on a weight or weight-for-weight basis.
20

21 Referring to Figs. 1 and 2, a particularly preferred embodiment of particulate
22 cosmetic gel carrier comprises relatively small agar particles or agar beads 10
23 having an average particle size measured in millimeters. The particles are small
24 enough for cosmetic use, and preferably do not exceed 10 mm. in diameter, on
25 average, but not so small as to penetrate the skin or skin pores. A minimum
26 diameter, on average, is about 0.05 mm. (50 microns). A preferred range of
27 particle sizes is from about 0.1 to 3.0 mm. in diameter, on average, with a more
28 preferred range being from about 0.25 mm. to about 1 mm. in diameter, on
29 average.

1 Preferred methods of producing the particles yield a well-focused size
2 distribution, so that it is preferred that at least 80 percent of the particles, more
3 preferably 90 percent of the particles, lie within a desired average particle size
4 bracket extending up to about 30 percent either side of a targeted average. If
5 desired, for particular applications, a more uniform product can be obtained by
6 mesh filtration.

7
8 Agar beads 10 are complexes of a continuous phase of agar gel 12 in a self-
9 supporting solid or semi-solid form with a restraining polymer 14. Dispersed
10 randomly throughout each agar bead 10 is a water-soluble, preferably polar,
11 restraining polymer 14, preferably a quaternized cationic polymer, such as
12 polyquaternium 24 or steardimonium hydroxyethylcellulose. Restraining
13 polymer 14 is entrapped in agar gel 12 so that it is not readily leached or
14 otherwise released therefrom so long as the bead 10 retains its integrity. Agar
15 beads 10 can serve as a cosmetic delivery system for various active agents 16
16 which are bound to restraining polymer 14, for example ascorbic acid, lactic acid
17 or papain, or alternatively they may be useful in their own right, without any
18 further active ingredient, for example to deliver an entrapped restraining
19 polymer, such as hyaluronic acid, a moisturizer, which has cosmetic or other
20 active properties of its own. There are numerous possible alternative substances
21 or materials to the preferred embodiments stated for agar gel 12, restraining
22 polymer 14, and active agent 16, some of which are set forth hereinbelow. Others
23 will be apparent to those skilled in the art.

24
25 As suggested schematically in Figure 2, agar beads 10 can be manually crushed
26 on the skin, preferably by an ordinary spreading or massaging action of one or
27 more of the user's fingers 18, (or hands or equivalent other body parts, or
28 implements), increasing the surface area of the agar beads 10 and bringing
29 restraining polymer 14 into contact with the surface of the skin where normal

1 skin constituents can release the active agent 10 from the restraining polymer 14,
2 permitting it to permeate into the outer layers of stratum corneum skin cells 20.
3 In Figure 2, skin cells 20 have been exaggerated in size for clarity.

4
5 Continued spreading and massaging by the user's fingers 18 spreads the agar gel
6 complex, with restraining polymer 14, over the skin surface where it can exercise
7 its active properties, such as moisturizing, if it has any. Alternatively, if the
8 polymer is substantially inert, along with the agar gel itself, the polymer will
9 suffer one of the usual fates of cosmetic residues of being rubbed or washed off
10 the skin or of being absorbed and enzymatically degraded or ultimately, if
11 sufficiently inert, excreted.

12
13 Several different physico-chemical mechanisms of action are available to release
14 active agents 16 from the restraining polymer 14 when the polymer 14 is exposed
15 to the skin environment by crushing and spreading the agar beads. Sweat and
16 sebum glands constantly discharge, respectively, moisture laden with various
17 ionics, notably sodium chloride, at low strength, and a mix of lipids with
18 phospholipids. The agar-polymer complex beads 10 of the invention are
19 sufficiently large that they do not penetrate normal skin pores, follicular
20 openings and the like. As the agar bead material is crushed and spread on the
21 skin, its surface area increases providing an extended interface between the gel-
22 polymer complex and any superficial skin moisture or lipids, initiating gradual
23 release of active agent 16.

24
25 The ionic strength of skin moisture can break ionic bonds with the restraining
26 polymer 14, encouraging migration of ionic active agents 16 to moist areas of the
27 skin. Alternatively, the normal acidity of the skin, pH about 5.5, may release
28 cationic actives 16 bound ionically to restraining polymer 14. In addition, natural
29 skin lipids, such as sebum, may release lipophilically bound active agents.

1 If the skin is dry, with time, the gel-polymer complex can permeate through the
2 skin moisture barrier constituted by the outermost keratinous layers of stratum
3 corneum cells 20, and by the lipophilic "mortar" in the intercellular spaces 22,
4 that bind cells 20 together, they encounter moisture and lipids to release actives.
5 Such action may be encouraged by enzymatic lysing of the gel or polymer. The
6 scope of the invention is not limited by the foregoing, or any other, theories or
7 contemplated mechanism of action, which are provided by way of explanation,
8 but only by the appended claims. What is significant is that the invention
9 provides a delivery system which can successfully deliver actives to the skin
10 surface and, if desired, protect those actives in cosmetic or other vehicles, during
11 formulation or on the shelf, or both.

12
13 Some substances and materials usable in the practice of the invention are
14 described in the following paragraphs. Others will be apparent to those skilled
15 in the art.

16
17 **Gel-forming agents:** A particularly preferred gel-forming agent for use in the
18 practice of the invention is agar, also known as "agar-agar". More properly
19 referenced "agarose," which is the neutral gelling fraction of agar (the other
20 being a sulfated non-gelling fraction "agaropectin"), the term "agar" is
21 nevertheless used herein in the same sense as "agarose". Agar is an example of a
22 gel-forming polysaccharide commonly used as a medium for electrophoresis and
23 chromatography. Agar is insoluble when dispersed as a dry solid in water at
24 low temperatures, however, it becomes soluble when heated to temperatures
25 over 70-90°C and forms a gel upon cooling. Agar is relatively expensive in
26 comparison with some other commonly used gelling agents, but is particularly
27 well suited for formulation with cosmetic vehicles, especially two-phase creams,
28 gels and lotions which are usually homogenized at an elevated temperature.
29 Agar gels are stable to both pH and moderate elevation of temperature.

1 Surprisingly, preferred embodiments of agar-polymer complex gel beads can be
2 formulated into cosmetic creams, employing aqueous phase ingredients and
3 temperatures as high as 80 °C, without losing their integrity, and while
4 continuing to protect contained actives. Agar gel beads are stable, once formed,
5 and are difficult to solubilize in aqueous media, even at elevated temperatures.
6 The beads of the invention are thus sufficiently durable to remain stable for the
7 relatively short period at elevated temperature, e.g. up to about 10 minutes,
8 required for homogenization of cream or other emulsions, and in fact should be
9 stable for up to about 30 or 40 minutes. In addition, ungelled agar solutions are
10 stable at temperatures as high as 100 °C which is advantageous for solids
11 loading, permitting high concentrations of active and restraining polymer to be
12 dissolved.

13
14 However, in preparing the agar-gel beads or formulating them into cosmetics,
15 care should be taken to avoid exposing heat-sensitive agents to excessive heat, by
16 adding them at lower temperatures, adding beads to cosmetic formulations after
17 emulsification or by exposing beads containing such heat-sensitive actives for
18 only short periods of time insufficient to be damaging.

19
20 While agar is a particularly preferred gel for use in the practice of the invention,
21 other gels meeting the requirements of the invention can be used. Such other
22 gels should be capable of forming dimensionally stable, self-supporting gel-
23 polymer complex particles that are stable under the conditions of formulation, if
24 any, (the particles themselves may constitute the end product), packaging and
25 storage, and which can be crushed, spread or otherwise dispersed on the skin or
26 nails of an end user to increase the surface area of the particles and disperse
27 contained active *in situ*. The beads are preferably not unduly tacky and do not
28 adhere to one another on contact. Preferred gels are water-soluble polymers that
29 are pH stable. Preferably also, they should be such as can yield polymer-

1 complex beads that are stable, when exposed with mixing, to an aqueous
2 environment at about 50 °C for at least 5 and preferably 15 minutes. Still more
3 preferably, the polymer complex beads produced should be stable, when
4 exposed with mixing, to an aqueous environment at about 80 °C, for at least 5,
5 and preferably 15, minutes.

6
7 Other such possible gels will be known or apparent to those skilled in the art, in
8 the light of the disclosure herein, and may include: synthetic polymers, such as
9 vinyl or acrylamide polymers, or copolymers; natural polymers, for example
10 polysaccharides, or proteins or synthetically modified ones of such polymers;
11 botanically derived gels; and may include gelling agents such as carbopol, a
12 common, low-cost petroleum-derived, cosmetic gel. However carbopol's gelling
13 characteristics depend on pH levels, so that it not a suitable protectant for many
14 actives for example alpha hydroxy acids.

15
16 It will be understood that the gel-forming agent selected for use in the practice of
17 the invention should not only satisfy the particle or bead forming requirements
18 described herein, but should also meet any requirements associated with the
19 intended cosmetic, pharmaceutical, medicament, or other end use of the bead.
20 Some other such gel-forming polymers are disclosed in Cini *et al.*, *supra*, see for
21 example, column 4, line 11 to column 6, line 30, the disclosure of which is hereby
22 incorporated herein by reference thereto.

23
24 **Restraining polymer.** As stated above, the restraining polymer employed in
25 practicing the invention has sufficient molecular weight to prevent egress of the
26 restraining polymer from the agar gel, and has retention groups to bind the
27 active agent to the restraining polymer for retention in the gel particles.
28 Preferably also, it is water-soluble to a sufficient extent that a desired proportion
29 can be co-dissolved with agar in an initial particle-forming step. The restraining

polymer used is preferably selected according to the desired active agent or agents to have one or more retention groups which will bind the active agent.

Pursuant to the invention, it has been discovered that polymers with an average molecular weight of about 100,000 daltons, and more, are unable to flow through a preferred agar gel matrix. However, certain polymers, especially polymers capable of interacting with the agar, may be adequately retained in an agar gel, for the purposes of the invention even although they have a lower average molecular weight, e.g down to 75,000 daltons, or even as low as 50,000 daltons.

There is no particular upper limit to the molecular weight of the restraining polymer, although it is contemplated that the average molecular weight will not exceed several million, e.g. 5 million daltons, but preferably does not exceed 1 million daltons. A preferred range for the average molecular weight is from 75,000 to 125,000 daltons.

Some preferred classes of restraining polymer are cationic polysaccharides and polypeptides or proteins. For example, some specific restraining polymers preferred for the practice of the invention are certain commercially available quaternized polysaccharides, especially celluloses, rich in quaternary groups, notably polyquaternium 24 available under the trademark QUATRISOFT LM-200 (Union Carbide Corporation), polyquaternium 11, available for example under the trade name GAFQUAT 755N (ISP Europe), and the CRODACEL Q (trademark) range of alkyl quaternary cellulose polymers (Croda, Inc.), notably laurdimonium hydroxyethylcellulose, sold under the trademark CRODACEL QL, cocodimonium hydroxyethylcellulose, sold under the trademark CRODACEL QM and steardimonium hydroxyethylcellulose, sold under the trademark CRODACEL QS. The CRODACEL Q (trademark) polymers belong to a class of polymers having repeating units of the following general nature:



1 where \underline{x} is often unspecified but may be taken to be under 10 and may be 0; R_1 is
2 commonly methylene; R_2 and R_3 are frequently methyl and R_4 is the characteristic
3 longer alkyl group, e.g. 10-30 carbon atoms such as lauryl, cocoyl or stearyl. The
4 polyquaternium 24 polymers lack the two hydroxyethyl substituents. Each
5 anhydroglucose unit can have a maximum of three ethoxy substituents, as
6 shown, but in practice, the average degree of ethoxy substitution will be
7 substantially lower so that the indication of di-hydroxyethyl substitution should
8 be regarded as a theoretical limit rather than a practical representation. Thus,
9 each repeating anhydroglucose or saccharide unit contains up to two
10 hydroxyethyl substituents and a quaternary ammonium group attached to the
11 polysaccharide nucleus via a short polyethoxy chain. Polyquaternium polymers
12 lack the longer alkyl group and the lipophilic character it confers.

13
14 Of particular importance is the quaternary nitrogen atom which provides a
15 cationic binding site for anionic actives. The R_4 alkyl chain can provide a
16 lipophilic anchor for lipid or lipophilic actives. the CRODACEL Q (trademark)
17 range of quaternized celluloses are more fully described in a product data sheet
18 entitled "Crodacel Q range" from Croda Chemicals Ltd., UK, the disclosure of
19 which is hereby incorporated herein by reference thereto. They are supplied as
20 somewhat hazy or opaque viscous concentrates intended for dilution and are
21 known as film-forming agents with particular application in hair shampoos and
22 conditioners, where their ability to be substantive to the hair, i.e. to attach
23 themselves to the hair in a substantive manner, without creating build-up, is
24 valuable. These and similar polymers suitable for use in the practice of this
25 invention are well known in the literature and are described, for example, in U.S.
26 Patents Nos. 5,135,748 (Ziegler *et al.*), 4,970,067 (Panandiker *et al.*), 5,288,484
27 (Tashjian) the disclosures of which are also hereby incorporated herein by
28 reference thereto.

29

1 Quantitatively, it is theoretically possible for each polar group to bind one acidic
2 molecule of the entrapped active, assuming the active molecule is small enough
3 to fit. In order to produce an end-user cosmetic suspension with a desirably high
4 concentration of active, the ionic bonding capacity should be as high as practical
5 and so must be the number of cationic groups bonded to the polymer backbone.
6 While ratios as low as 0.2 or close to the theoretical limit of 2.0 may be useful, an
7 average ratio of 0.5 moles to 1.5 moles of quaternary groups per glucose unit is
8 preferred to provide a high loading capacity of the active to the agar bead
9 without too high of a proportion of polymer to agar. In practice, a commercially
10 available ratio of 1.2 moles of quaternary groups per glucose unit was used, this
11 being the approximate number for steardimonium hydroxyethylcellulose, a
12 strong anion exchanger, can be used, as well as, weak anion exchangers (tertiary
13 amines) and cation exchangers, either strong (sulfonate or phosphate groups) or
14 weak (carboxyl groups).

15
16 Other polysaccharide polymers which, when suitably modified, can be used
17 include starch, cellulose, chitosan and karageenan. Other polymers can be used
18 such as modified proteins, polypeptides of adequate molecular weight, or non-
19 biological polymers (e.g. acrylates). Protein-based or biological polymers may
20 bring allergenicity problems, depending upon their heterogenicity, and are
21 accordingly not preferred for use in the practice of the invention. However,
22 relatively homogenous polyamino acids, e.g. polylysine, have low
23 immunogenicity and are more suitable for use as the restraining polymer of the
24 invention. The amino acid monomer, e.g. one or more of the amino acid elements
25 of natural polypeptides, can be selected to provide a desired retention unit,
26 having desired binding characteristics with a particular target active, as will be
27 apparent to those skilled in the art. Thus, at suitable pH levels, the basic, distal
28 amino groups of polylysine or polyarginine can provide cationic retention
29 moieties for anionic actives, while the distal carboxyl moieties of polyaspartic

1 acid or polyglutamic acid, can provide anionic retention moieties for cationic
2 actives.

3
4 The retention groups do not necessarily have to be covalently bound to the
5 restraining polymer backbone, but may be provided as components of molecules
6 complexed, or otherwise bound, or associated with the restraining polymer in a
7 manner facilitating the retention of one or more desired active agents within the
8 gel beads. The term "restraining polymer" as used herein includes such polymer
9 complexes or associations. Accordingly, in manufacturing the beads, separate
10 ingredients may furnish the polymer backbone and the retention groups. For
11 example, the polymer backbone may be provided by a water-soluble or
12 hydrolyzed protein, e.g. hydrolyzed whole wheat protein, such as available
13 under the trade name HYDROTRITICUM 2000 (Croda Chemicals Ltd., UK), and
14 cationic groups may be furnished by a quaternary amine salt having a substantial
15 lipid character, e.g. behentrimonium methosulfate combined with cetearyl
16 alcohol, available under the trade name INCROQUAT BEHENYL TMS (Croda
17 Chemicals Ltd., UK), a self-emulsifying waxy substance. These latter two
18 materials may be employed in relative anhydrous weight proportions of from
19 about 1:10 to about 5:1, preferably about 5:1 to about 1:1 of hydrolyzed whole
20 wheat protein to the commercially available INCROQUAT BEHENYL TMS
21 product, to provide the restraining component of the invention. Other,
22 equivalent products can be used to provide a comparable distribution of cationic
23 (or possibly anionic, depending upon the active agent) groups in the resultant
24 restraining polymer.

25
26 Other suitable restraining polymers which can meet the requirements of the
27 invention will be known or apparent to those skilled in the art, based upon the
28 teachings of the disclosure herein. Mixtures of different restraining polymers
29 can also be used.

1 **Actives:** Some examples of classes of dermally active, or dermally effective
2 substances having biological or cosmetic activity, which can be topically
3 delivered employing the delivery systems of the invention include: antioxidants
4 including botanically derived polyphenols, for example procyanidin oligomers;
5 free radical scavengers; topically active enzymes, for example, antibacterials,
6 such as glucose oxidase, antioxidants such as superoxide dismutase, and
7 proteolytic enzymes such as bromelain and papain, (useful for enzyme peeling);
8 other enzymes such as the DNA repair enzymes described above; exfoliative
9 retinoids, such as retinol and retinol esters including retinol acetate, vitamin A
10 palmitate; purified plant extracts and plant proteins; vegetable oils, for example,
11 grape seed, sunflower, safflower and jojoba oil; essential fatty acids, such as
12 linoleic acid, linolenic acid and arachidonic acid; animal proteins, for example
13 collagen, elastin and keratin; moisturizers, such as hyaluronic acid and other
14 glycosaminoglycans; whitening agents such as arbutin; ultraviolet light filters;
15 coated or uncoated organic and inorganic pigments such as titanium, zinc, and
16 iron oxides and anti-actinic suspensions or dispersions of such inorganic oxides;
17 melanin or a sepia ink extract; other colorants or dyes, and perfumes.

18
19 While pigments and perfumes may have a role in enhancing the esthetic appeal
20 of the carrier gel beads in which they are incorporated, they may also perform
21 cosmetic functions when the gel beads are applied to the skin or other
22 endogenous surfaces, for example, the nails or hair and then crushed,
23 commencing controlled release of the actives. The release can, to some extent, be
24 user controllable. Thus, for example, a user may firmly spread a body cream
25 containing perfume-loaded gel-complex beads according to the invention, until
26 they detect enough perfume is released or a rouge, makeup, foundation or other
27 pigmented cosmetic, until the color is to their liking. The carrier beads and the
28 respective proportions of their components may be adjusted to provide
29 continued release to sustain the color or perfume intensity. In addition, the user

1 may, with small, hard-to-see beads, refresh the active by further crushing and
2 spreading residual uncrushed gel beads, at a later time.

3
4 In general, any active can be used that binds satisfactorily to the restraining
5 polymer and can be released by contact with the skin. Many novel formulations
6 and enhancements of known cosmetics that can be obtained by supplementing
7 them with labile actives carried within and protected by the polymer-gel
8 complex beads of the invention, will be apparent to those skilled in the art. One
9 such product comprises a mixture of actives providing a novel prophylactic and
10 therapeutic treatment for solar exposure comprises an ultraviolet absorbent or
11 screening agent, for example titanium dioxide, an antioxidant, for example
12 vitamin E, and a DNA repair enzyme, incorporated into agar-polymer complex
13 beads, according to the invention. If desired, a melanocyte stimulant could be
14 included. Such beads could be used *per se*, or incorporated into traditional
15 creams or lotions.

16
17 **Preferred Actives:** Some examples of particularly preferred actives for delivery
18 by the gel carrier particles of the invention are: ascorbic acid (vitamin C), alpha-
19 tocopherol (vitamin E), tocopherol acetate (vitamin E acetate), purified papain
20 extract, beta-carotene, green tea extract rich in polyphenols, purified extracts of
21 procyanidolic oligomers from grape seed or pine bark, monoazoic dye e.g. D&C
22 orange, xanthenic dye (disodium salt), cinnamic acid and
23 octylmethoxycinnamate.

24
25 Surprisingly, all of these materials can be effectively bound to a modified starch
26 restraining polymer containing quaternary ammonium groups, incorporated in
27 the protective gel carrier particles of the invention, and then formulated into a
28 cosmetic cream so that they retain their activity, or cosmetic properties, when
29 applied topically. Furthermore, multiple such actives can be similarly bound to

1 a suitable restraining polymer and incorporated in protective gel carrier
2 particles, to deliver their desired properties to end users in topical formulations,
3 for example, an antioxidant combination of vitamins C and E, colored with three
4 colorants, and one or more colorants combined with papain, or other such
5 preferred active.

6
7 One preferred class of actives is anionic, a particularly preferred restraining
8 polymer to which the actives bind being a modified polysaccharides containing
9 quaternary ammonium groups which are cationic and are able to form stable
10 ionic bonds with many anionic actives.

11
12 **Water.** Water is also a significant ingredient of the carrier particles of the
13 invention, being the medium through which colloidal agar particles are
14 dispersed to provide a semi-solid or nearly solid gel. Other aqueous media, or
15 possibly, polar alcohols or glycols, may substitute for water. In preparing the
16 agar beads of the invention, agar and other ingredients are mixed with water and
17 injected through a needle as a warm solution or dispersion, at a speed controlled
18 to generate drops, then cooled to set the gel.

19
20 **Proportions.** The proportion of solids to water should be sufficient to dissolve or
21 disperse the solids and to ensure they will remain in solution or dispersed until
22 desired gel formation in the oil medium, *after* the droplets leave the injection
23 needle.

24
25 Preferably the solids comprise from about 0.5 to about 40 percent by weight of
26 the solution or dispersion and more preferably from about 1.5 to about 25
27 percent by weight. The relative proportion of restraining polymer 14 to agar 12
28 can be as low as 1:10, but to obtain a satisfactory loading of active agent 16
29 (which can, in certain instances, be the polymer itself, e.g. hyaluronic acid) a

1 proportion of at least 1:1, up to about 10:1 restraining polymer 14 to agar 12, is
2 desirable. Preferably, a proportion of from about 2:1 to about 6:1 is used.

3
4 The proportion of active agent 16, assuming such to be additional to the
5 restraining polymer 14, will usually be made as high as practical, without
6 affecting the integrity of the particle or causing unacceptable instabilities in
7 storage. The maximum practical loading of active, a desirable objective, will
8 vary substantially, depending upon the nature of active agent 16 and will usually
9 be related to the quantity of restraining polymer 14. Depending upon the
10 potency of the active, and other factors such as its physical form, the proportion
11 of active agent to restraining polymer may range from about 0.01:1 to about 10:1,
12 preferably from about 0.1:1 to about 5.0:1. Preferably also, the active agent
13 comprises from about 0.01 to about 20 percent of the solution, or dispersion, at
14 the injection needle, more preferably about 0.1 to about 10 percent.

15
16 The foregoing relative proportions are, as previously stated, based on weight,
17 and are also based on the ingredients of the solution or dispersion at the injection
18 needle. With proper manufacturing or production procedures, these
19 proportions should largely be reflected in the end product agar complex gel
20 beads themselves, but variations may occur.

21
22 **Cosmetic formulations.** Cosmetic formulations, diluents or cosmetic vehicles are
23 compositions applied externally to the skin, hair or nails for purposes of
24 cleansing, beautifying, conditioning or protecting the body surface. Cosmetic
25 formulations include but are not limited to water-in-oil or oil-in-water emulsions
26 in cream or lotion form, sunscreens, toners, astringents, facial make-ups,
27 powders, and skin cleansing compositions. The recipes for such compositions
28 are well known to those skilled in the art and can be found in many publications
29 in the field. A brief summary of some such cosmetic "diluents" that can be used

1 in the practice of the invention appears in Wolf *et al.* U.S. Patent 5,449,519, for
2 example at column 4, line 25 to column 6, line 56, the disclosure of which is
3 hereby incorporated herein by reference thereto. The gel-complex particles of
4 the invention are generally suitable for incorporation into such cosmetic
5 compositions or "diluent" and the invention extends to the resultant gel-
6 complex particle containing compositions which have beneficial properties
7 arising from the presence of the gel-complex particles, for example new active
8 ingredients, new concentrations of active ingredients, or simply better delivery
9 of active ingredients with reduced loss of activity.

10
11 The gel beads of the invention can be used in such cosmetic compositions in any
12 desired concentration or proportion that will provide an effective amount of
13 active agent upon application, for example from 0.1 to 90 percent by weight of
14 the total composition, preferably from 1 to 50 percent, and more preferably from
15 5 to 25 percent by weight of the total composition.

16
17 **Manufacture.** As shown in Figure 3, it is known to make agar gel beads by
18 dissolving granular agar in deionized or distilled water heated to an elevated
19 temperature sufficient to dissolve the agar, using a proportion of agar to water
20 effective to form a gel at lower temperatures, cooling the hot agar solution to a
21 suitable intermediate temperature above the gelling point of the agar solution,
22 typically about 30 °C, and injecting the cooled solution through an injection
23 needle, sized according to the desired agar bead size, into a hydrophobic liquid
24 maintained at a temperature suitably below the agar gelling point for bead
25 formation, at a rate of injection controlled to favor bead formation. As indicated
26 in the illustrative example of Figure 3, the dissolved agar is cooled to about 50 °C
27 and injected into an oil medium, e.g. a paraffin bath, at about 2.5 °C, whereupon
28 the agar gel beads solidify as they leave the injection needle.

29

1 In the method of the invention, a suitable restraining polymer, and the active
2 agent, if any, dissolved or dispersed in water or an aqueous solvent system, are
3 mixed with the agar solution before injection into the hydrophobic liquid.
4 Suitable restraining polymers, and many actives, are generally temperature
5 stable and can be mixed with the agar granules and heated to the elevated
6 temperature to provide a clear solution of all ingredients. Less stable actives, for
7 example, enzymes, can be introduced to the agar-polymer solution at the
8 intermediate temperature, preferably in aqueous solution or suspension.

9
10 The temperatures of both the agar mixture and the paraffin bath are chosen and
11 adjusted according to the type of bead being produce, i.e. its constituents, toward
12 the goal of providing separable, pourable beads which can be crushed or spread
13 on the skin. In particular, they are adjusted to ensure that the viscosity of the hot
14 agar mixture is low enough to permit the mixture to be pumped through the
15 injection needle. The viscosity will vary with different bead formulations, being
16 increased by higher concentrations of ionic actives.

17
18 Other methods of forming gelatinous beads will be known or apparent to those
19 skilled in the art, and may be adapted to the purposes of the invention. For
20 example, instead of injecting drops of warm agar solution into a cold oil bath, the
21 warm solution may be dripped from above on to the surface of cold oily
22 medium. A particularly efficient process comprises mechanically dispersing the
23 warm solution in a cold immiscible oil or the like using an agitator. The rate, or
24 degree of agitation determines the size of the gel beads produced.

25
26 If desired the active agent and the restraining polymer can be premixed to foster
27 bonding of the active to the restraining polymer, in a preliminary step.

28 Lipophilic acids, can if desired, be bonded to the restraining polymer in a
29 preliminary mixing step employing a lipophilic solvent which is evaporated or

1 otherwise removed prior to mixing with the agar solution.

2

3 The resultant beads comprise a complex of active-loaded restraining polymer
4 entrapped in an agar matrix. The beads are soft, clear, glossy, odor-free and
5 esthetically appealing, pH-stable and temperature stable to temperatures up to
6 about 80 °C. The hardness, or preferably softness of the beads is preferably
7 carefully chosen, by appropriate selection of processing parameters, according to
8 the bead components, so that the beads are hard enough to be conveniently
9 handled, transferred from drums to formulation vessels, and the like, and hard
10 enough to resist breakdown in mixers or homogenizers, yet soft enough to be
11 crushed on the skin, and preferably sufficiently soft to be spread and
12 “disappear”.

13

14 A principal parameter affecting the hardness is the agar concentration (higher
15 concentrations form harder beads), but oily actives will soften the beads and the
16 concentration and composition of the restraining polymer can also affect the
17 hardness of the bead. These parameters are preferably selected and controlled to
18 provide the desired hardness, which is that of a soft, pleasant crushable feel.

19

20 Referring to the manufacturing process illustrated schematically in Figure 4, agar
21 granules 12, restraining polymer 14 and stable active agent 16, if used, are
22 dissolved and, if appropriate, dispersed, in a mixing step 24 in deionized or
23 distilled water, conducted at an elevated temperature, preferably between about
24 70 and about 100 °C, more preferably between about 85 and about 95 °C, or about
25 90°C. Upon heating, the suspension becomes a clear solution.

26

27 Optionally, the solution or dispersion is cooled in a cooling step 26 to an
28 intermediate temperature above the gelling point of the solution or dispersion
29 where less heat must be lost from the solution or dispersion to precipitate

1 gelation. The intermediate temperature may range from about 40 to about 70 °C,
2 preferably from about 50 to about 60 °C. Less stable actives, for example
3 enzymes, dissolved or dispersed in water are incorporated in, and mixed with,
4 the agar-polymer solution at the intermediate temperature to avoid detrimental
5 effects of the higher temperature. Enzyme-containing solutions should be kept
6 near to about 50 °C to avoid denaturing which may occur at temperatures
7 around 60 °C.

8
9 Preferably, the solution is temperature stabilized, at the intermediate
10 temperature, for example, using a water jacket or bath, maintained at a
11 temperature of about 50 °C, in temperature-stabilization step 28.

12
13 The liquid solution or dispersion is then pumped through a needle submerged in
14 a liquid paraffin oil bath maintained at a temperature below the gelling point of
15 the solution or dispersion, namely below about 30 °C, preferably below about 25
16 °C, more preferably about 0 to 10 °C, while mixing, in oil injection step 30.

17 Because water and oil are immiscible, the pumped solution of warm agar,
18 polymer and active, form droplets when extruded into the oil. The low
19 temperature of the oil "freezes" the droplets in shape, causing the agar medium
20 to gel into agar-polymer complex beads 10. Alternatively the hot agar solution,
21 from step 24, may be directly introduced to the cold oil at a rate such as to
22 provide adequate cooling to provide bead formation.

23
24 The agar-polymer complex beads 10 are then separated, washed to remove the
25 paraffin oil, filtered and dried, in separation step 32.

26
27 Referring to Figure 5, an alternative method of the invention does not require
28 needle injection of the agar-restraining polymer solution into the cold oil bath.
29 Preparation of the hot or warm agar-polymer solution in mixing step 24 and

1 optional cooling step 26, with addition of active agent 16 at a suitable point, is
2 similar to the process depicted in Figure 4. The warm aqueous phase agar
3 solution (or dispersion) is then introduced into a substantial excess of cold oil
4 with agitation, for example by means of a rotating paddle. Rather than the
5 relatively slow and more difficult process of feeding the solution through a
6 submerged hollow needle, a relatively rapid, simple pouring step suffices to
7 introduce the aqueous phase to the colder oil. The components of the two phases
8 are selected to be immiscible so that beads will form as the dispersion is agitated.
9 The average size of the beads can be controlled by the speed of agitation and it is
10 preferably under 5 mm, more preferably from about 2 microns to about 1.5 mm..

11
12 Large gel particles or beads, up to approximately 2 mm in diameter, can be
13 colored, filled with actives and formulated in a transparent gel, the colorants and
14 actives being incorporated in the injection solution or dispersion. Different sized
15 beads can be produced by adjusting the size of the needle diameter or the
16 agitation speed of the oil bath, higher speeds producing smaller beads.

17
18 Some non-limiting examples of the practice of the invention will now be
19 described by way of illustration.

20 EXAMPLE 1

21 Preparation of Agar Complex Beads using Polyquaternium 24

22 1.5 g of agar granules (OSI-France) with a gelling point of about 33 ° C and 1.5 g
23 of polyquaternium 24 [QUATRISOFT LM-200 trademark Union Carbide
24 Corporation (Amerchol-France)] are mixed in 97 g of distilled water and heated
25 to 90°C. The suspension becomes a clear solution at this temperature and it is
26 then allowed to cool to 50°C in a water bath. The solution is then pumped
27 through a needle by means of a peristaltic pump (Bioblock-France) and the
28 needle is placed into a liquid paraffin oil bath maintained at 5°C while mixing
29 (250 rpm). The pump flow rate is adjusted to 2.5 ml/minute and the liquid is

1 injected into the oil bath. Gel beads are formed in the oil phase and their size
2 depends upon the inner diameter of the needle. For this example, two different
3 sized needles were used: 0.45 x 12 mm or 0.8 x 50 mm (inner diameter x length).
4 The gel beads are separated by filtration on a 0.2 mm screen and extensively
5 washed with water. In this example, 2mm diameter beads are typically formed.
6 Smaller beads are formed using higher mixing rates (e.g. 1200 rpm) while smaller
7 needle diameters help maintain small diameter. The gel beads formed are
8 smooth, shiny and soft. Surprisingly, the presence of the restraining polymer
9 does not significantly alter the ability of the agar to gel and form stable beads
10 when cooled in oil.

11 12 **EXAMPLE 2**

13 Preparation of Agar Complex Beads using Hyaluronic Acid as Anionic 14 Copolymer

15 The procedure of Example 1 is followed except hyaluronic acid (Soliance-France)
16 is mixed with the agar instead of polyquaternium 24. The beads formed by this
17 procedure are suitable for use either as a moisturizer, delivering hyaluronic acid,
18 or as a delivery system for cationic actives attached or bound to the hyaluronic
19 acid.

20 21 **EXAMPLE 3**

22 Preparation of Agar Complex Beads using Steardimonium 23 Hydroxyethylcellulose

24 The same procedure as in Example 1 is used, except that 7.5 g of steardimonium
25 hydroxyethylcellulose (CRODACEL QS, trademark, Croda, Inc.) is substituted
26 for the polyquaternium 24. Similar beads are obtained after extrusion into a 5°C
27 oil bath.

28 29 **EXAMPLE 4**

1 Preparation of Agar Complex Beads Containing an Enzyme, Papain

2 1.5 g of agar and 7.5 g of steardimonium hydroxyethylcellulose are mixed in 56 g
3 of distilled water and heated to 90°C under mixing to obtain a clear solution.
4 The mixture is allowed to cool at 60°C and 5 g of papain in 30 g of distilled water
5 is added to the solution. The mixture is maintained at 50°C in a water bath, then
6 injected into liquid paraffin oil at 5°C under mixing (250 rpm). 2 mm diameter
7 beads are formed, separated and washed with water.

8
9 **EXAMPLE 5**

10 Preparation of Agar Complex Beads Containing a Colorant

11 Following the procedure of previous examples, 1.5 g of agar, 7.5 g of
12 steardimonium hydroxyethylcellulose and 0.5 g of FD&C Blue (Colorants
13 Wackherr-France) are dispersed together in 90.5 g of distilled water. The 2 mm
14 diameter beads are formed in the oil bath, then separated and washed with
15 water.

16
17 **EXAMPLE 6**

18 Preparation of Agar Complex Beads Containing a Plant Extract

19 Following the procedure of previous examples, 0.6 g of agar, 0.2 g of
20 steardimonium hydroxyethylcellulose (trademark), 1.0 g of polyquaternium 24
21 and 1.0 g of green tea extract (Rahn AG Switzerland) are dispersed in 30 g of
22 distilled water and heated to 90°C under mixing. 2mm diameter beads are
23 formed in the oil, then separated and washed with water.

24
25
26 **EXAMPLE 7**

27 Preparation of Agar Complex Beads Containing a Lipophilic Active, Beta-
28 Carotene

29 1.5 g of agar is dispersed in 70.5 g of water and heated to 90°C under mixing to

1 obtain a clear solution which is allowed to cool at 60°C. Then 7.5 g
2 steardimonium hydroxyethylcellulose and 0.5 g of β -carotene (Cooperation
3 Pharmaceutique Française-France) predispersed in oil, is dispersed in 20 g of
4 distilled water and mixed with the above solution. The restraining polymer
5 facilitates dispersion of the hydrophobic β -carotene. The mixture is maintained
6 at 50°C and injected through a needle (0.45 x 12mm) into liquid paraffin oil at
7 5°C under mixing. The beads produced containing the β -carotene have an
8 average diameter of 2mm.

10 EXAMPLE 8

11 Preparation of Agar Complex Beads Containing both Hydrophilic and Lipophilic

12 Actives: Vitamin C and Vitamin E

13 Following the procedure of Example 7, 1.5 g of agar, 7.5 g of steardimonium
14 hydroxyethylcellulose, 7.5 g of ascorbic acid (Cooperation Pharmaceutique
15 Française-France), 2.5 g of α -tocopherol (Fluka-Switzerland) are mixed in 81 g of
16 distilled water. 2 mm diameter beads containing vitamins C and E are obtained
17 in the oil phase, then separated and washed with water.

19 EXAMPLE 9

20 Preparation of Agar Complex Beads Containing a Pigment

21 Following the procedure of Example 7, 1.5 g of agar, 1.5 g of steardimonium
22 hydroxyethylcellulose, 5 g of titanium dioxide (ADF Chimie-France) and 2.5g of
23 iron oxide (Kobo Products USA) are mixed in 89.5 g of distilled water. 2 mm
24 diameter beads containing the pigment are formed in the oil phase, then
25 separated and washed with water.

27 EXAMPLE 10

28 Modification of the Preparation Method for Agar Complex Beads

29 Following the procedure of the previous Examples, a clear agar solution with

1 various additional ingredients, as recited, is maintained at 50°C, then pumped
2 through a needle. However, in this example, the needle is placed 10 cm above
3 the surface of the paraffin oil bath. Individual droplets are formed in air and fall
4 into the cooled liquid, generating beads. The beads have the same appearance as
5 the above described beads but their average size also depends upon the agitation
6 speed of the oil bath. 0.5 mm to 2 mm diameter beads can be generated using the
7 same type of needle with speed rates ranging from 100 rpm to 250 rpm. The gel
8 beads formed are smooth, soft and shiny.

10 **Example 11**

11 Preparation of Agar Complex Beads by Dispersion with Agitation

12 1.5 g of agar-agar, 7.5 g of aqueous Crodacel-QS (containing 1.5 g of PG-
13 hydroxyethylcellulose stearyldimonium chloride) are mixed with 91 g of water
14 and are heated to a temperature above 80°C for 15 minutes. The mixture is
15 cooled to 50°C and poured into a 1000 ml beaker containing 350 ml paraffin oil at
16 10°C, while mixing the oil phase with a motor and a U-shaped paddle at about
17 200 rpm. Approximately 1-millimeter beads of the aqueous phase are formed in
18 the oil phase and, the low temperature of the oil induces gelling. After about 10
19 minutes, the oil phase is filtered on a 500 micron stainless steel sieve and the
20 beads are thoroughly washed with water.

22 **Example 12**

23 Preparation of Vitamin-E-Loaded Agar Complex Beads by Dispersion with 24 Agitation

25 In this example, the entrapped compound, vitamin E, is heat sensitive and would
26 be damaged if heated to 80°C. Accordingly, the agar solution is cooled before
27 adding vitamin E. 1.5g agar-agar are mixed with 50 g of water and heated over
28 80°C for 15 minutes. Separately, 7.5 g of aqueous Crodacel-QS (containing 1.5 g
29 of PG-hydroxyethylcellulose stearyldimonium chloride) are mixed with 2 g of

1 alpha-tocopherol (Roche, Switzerland) and with 39 g of water. The agar mixture
2 is cooled to about 60°C and the Crodacel QS mixture is added. The resultant
3 mixture is further cooled to about 50°C and poured into a 1000 ml-beaker
4 containing 350 ml paraffin oil at 10°C, while mixing the oil phase with a motor
5 and a U-shaped paddle at about 200 rpm. Approximately 1-millimeter beads of
6 the aqueous phase are formed in the oil phase and, the low temperature of the oil
7 induces gelling. After about 10 minutes, the oil phase is filtered on a 500 micron
8 stainless steel sieve and the beads are thoroughly washed with water.

10 Example 13

11 Preparation of Agar Complex Beads Using Polyquaternium 11

12 The procedure of Example 11 is repeated except that 10 grams of a 20% aqueous
13 solution of polyquaternium-11 (Gafquat 755N) is substituted for the Crodacel-QS
14 solution.

16 Example 14

17 Preparation of Agar Complex Beads Using a Combination of Hydrolyzed Wheat
18 Protein with Cetearyl alcohol and Behentrimonium Chloride as a Cationic

19 Restraining Polymer

20 1.5 g agar-agar are mixed with 50 g of water and the preparation is heated to at
21 temperature in excess of 80°C for 15 minutes. 1.5 g of Incroquat Behenyl TMC
22 (behentrimonium methosulfate combined with cetearyl alcohol) are heated to
23 80°C. 6 g of water are separately heated to 90°C and slowly added to the melted
24 Incroquat Behenyl TMC and mixed for 15 minutes to obtain an emulsion. 0.5 g
25 of hydrolyzed wheat protein are added to the emulsion. which is cooled to 50°C.
26 When the agar-agar solution has cooled to 60°C, it is mixed with the protein-
27 containing Incroquat Behenyl TMC emulsion. 40.5 g of water are added, the
28 product is mixed and poured into an oil phase comprising 350 ml paraffin oil in a
29 1000 ml beaker, under mixing, 200 rpm). The beads are formed and sieved as

described in Example 11.

The gel beads formed by the methods of Examples 11-14 are smooth, soft and shiny with an attractive appearance and little or no odor. They are stable at room temperature and can be readily crushed on the skin enabling the bead interiors to be spread topically, with a pleasant cool feel.

ACTIVITY TEST

Activity of Ascorbic Acid after Entrapment within Agar Complex Beads

To determine if an active remains stable after its entrapment within mixed-agar beads, the activity of the ascorbic acid is measured by a DPPH test. In this test, 2,2 diphenyl-1-picrylhydrazyl (DPPH), a stable free-radical that exhibits an absorption band at 515 nm (violet color) which disappears upon reduction by an anti-free-radical agent.

Ascorbic acid is entrapped within the mixed-agar beads as set forth in the procedure in Example 8. Three 2 mm diameter beads containing an average ascorbic acid content of 2.25 mg and weighing approximately 30 mg each, were added to 3.5ml of methanolic DPPH solution (DPPH concentration 0.6×10^{-5} mol).

The beads were crushed in the test tube and the violet coloration attached to the DPPH disappeared within a few seconds. The experiment demonstrated that ascorbic acid entrapped in a complexed agar beads according to the invention retains its free radical scavenging activity.

Many materials can be added to the gel system, including fragrances and colorants, so long as they do not prevent satisfactory gel formation. However, care may be required with regard to liquids too much of which may impair the

1 physical stability of the gel beads. Preferably, the proportion of liquid in the gel
2 system additional to agar, restraining polymer and active agent is selected so
3 that gelling is not prevented. While excesses of water may result in soft or
4 poorly defined beads that are acceptable for some purposes, certain organic
5 solvents may prevent bead formation. In particular, it is preferred to avoid
6 excess proportions of organic solvents such as dipropylene glycol or butylene
7 glycol that are often used in fragrances. The following comparative Example A
8 demonstrates this point.

9
10 **Comparative Example A**

11 *Non-gelling Agar Complex Composition*

12 Example 1 is repeated using 1.5 g of agar granules, 7.5 g of CRODACEL QS
13 (trademark, Croda, Inc.), containing 1.5 g PG-hydroxyethylcellulose
14 stearyldimonium chloride, 97 g. of water, or other quantity sufficient for bead
15 formation in the absence of organic solvent, and 10 g dipropylene glycol. No
16 significant beading occurs.

17
18 **Comparative Example B**

19 *Other Non-gelling Agar Complex Compositions*

20 Comparative Example is repeated using solvated fragrance or butylene glycol in
21 place of the dipropylene glycol. Again, no significant beading occurs.

22
23 **Comparative Example C**

24 *Further Non-gelling Agar Complex Compositions*

25 Comparative Example A is repeated using pigments or active ingredients, as
26 described herein. Again, no significant beading occurs.

27
28 Since such solvents can perform useful functions in a gel bead system, for
29 example as vehicles for fragrances, it would be desirable to solve the problem of

1 forming a satisfactory gel in the presence of such solvents. Pursuant to the
2 present invention, this problem can be solved by providing the solvent or other
3 material in its own carrier system to protect the gel medium from the effect of the
4 solvent.

5
6 To this end, it has been discovered pursuant to this aspect of the invention that
7 such gel-inhibiting solvents can be effectively trapped in porous inert particles,
8 for example silica spheres, or porous microspherical inert polymers, such as
9 polyethylene or polypropylene which particles provide an effective carrier
10 system for the solvent and surprisingly, do not themselves interfere with gel
11 formation. Such particles are preferably at least one or two orders of magnitude
12 smaller than the gel beads in which they are incorporated, being for example
13 from about 0.5 to about 100 microns in diameter, preferably from about 1 to
14 about 30 microns and more preferably from about 3 to about 12 microns in
15 diameter. Suitable adsorbent silica particle products are supplied by Kobo
16 Products, Inc. , South Plainfield, New Jersey, USA.

17
18 Pursuant to this aspect, the invention provides a method of making gel beads, or
19 other gelled product, especially a gelled product intended for incorporation into
20 a cosmetics product, the method comprising adsorbing a gel-inhibiting solvent
21 on porous silica particles, or the like and dispersing the solvent-laden particles in
22 a gelling medium, the gelling medium comprising a solution or dispersion of a
23 suitable gelling agent, for example, an aqueous solution of agar, the preferred
24 gelling agent described herein. The gelling medium is then formed into the
25 desired gelled product as described herein, or as otherwise apparent to those
26 skilled in the art.

27
28 It will be understood by those skilled in the art that this aspect of the invention
29 has general application to enable a wide variety of solvents or other liquids to be

1 incorporated into a gelling system by loading the solvent into protective carrier
2 particles.

4 **Example 15**

5 *Formation of Agar Beads with Solvent*

6 10 g dipropylene glycol or a comparable fragrance solvent are mixed in a beaker
7 or other vessel, with 1.6 g oil-absorbent silica shells (Kobo Products, NJ, apparent
8 density 0.5-1.0 grams per cubic inch, oil absorbency from 550-700 g/110 g) to
9 obtain a thick slurry or paste-like product. The thick product is dispersed in 7.5
10 g of CRODACEL QS (trademark, Croda, Inc.), containing 1.5 g PG-
11 hydroxyethylcellulose stearyldimonium chloride, as described above in
12 connection with the addition of active agents. A hot aqueous agar solution,
13 containing 1.5 g of agar granules dissolved in 97 g. of water, or other quantity
14 sufficient for bead formation in the absence of organic solvent, is added and the
15 mixture is injected or dispersed in cold oil to yield well-formed, stable beads,
16 with a good and consistent texture and size.

18 **Example 16**

19 *Agar Complex Beads Employing Quaternized Silk Hydrolysate*

20 Example 1 is repeated employing, as a restraining polymer, an equivalent
21 amount of quaternized silk hydrolysate, PROMOIS (trademark) S-CAQ (Seiwa
22 Kasei Co., Ltd.). Comparable results are obtained.

24 According to another embodiment of gel bead manufacturing method according
25 to the invention it has been found that gel beads can advantageously be formed
26 by entraining a liquid source of hot gel solution in a controlled flow of a cool oil
27 stream, preferably moving with an approximately constant velocity.

29 Referring to Figure 6, In a preferred embodiment of the method, the hot gel

1 solution is supplied in the direction of arrow A1 to a venturi tube 40 having an
2 internal diameter ID_1 . Venturi tube 40 is supported in a side branch 42 of a
3 conduit 44 having an internal diameter ID_2 through which cold oil flows in the
4 direction of arrow A2, drawing gel solution from venturi tube A1. Side branch
5 42 is shown as extending perpendicularly to conduit 44. This apparatus can
6 provide consistent high quality bead formation with a sharp cutoff of the
7 forming bead from venturi tube 40. However, other angles could be employed.
8 For example, venturi 40 could be at an acute angle of up to 45° , delivering the gel
9 solution in the direction of flow of the cold oil. Alternatively, the tip 46 could be
10 turned in the oil flow direction. However, such configuration may impede
11 efficient breaking off of beads 48 from the stream of gel solution.

12
13 The bead size is related to the internal diameter ID_1 of venturi tube 40 and also
14 to the oil flow rate, higher oil flow rates generating smaller beads and *vice versa*.
15 Since rapid cooling of the gel solution is desirable to promote quality bead
16 formation, both the flow rate of the oil and the diameter ID_2 of conduit 44 are
17 preferably greater than the flow rate of the gel solution and the diameter ID_1 of
18 venturi tube 40. Preferably, diameter ID_2 is at least twice that of ID_1 , more
19 preferably at least five times and possibly as much as ten times as large. Thus,
20 the cross-sectional area of conduit 44 can be from 4 to 100 times, preferably 4 ,
21 and more preferably 25 times the cross-sectional area of venturi tube 40.
22 Preferred oil flow rates are also much higher than gel solution rates, for example
23 at least twice as high, more preferably four to twenty times as high. For small
24 beads oil flow rates may be 50 times higher. In general, the flow rate of the gel
25 solution will depend upon its viscosity.

26
27 Some exemplary quantities employ a venturi tube 40 with an ID_1 of about 0.8
28 mm and an oil flow conduit 44 with and ID_2 of about 8 mm. Employing an agar
29 solution, as described herein, the agar solution flow rate can be from about 2.5 to

1 6.2 ml/min. Oil flow rates can vary between about 10 and about 300 ml/min.
2 with lower rates being useful for making larger beads of about 2.8 to about 4 mm
3 diameter, and the higher flow rates being useful for making smaller beads of
4 about 0.4 to about 0.7 mm diameter.

5
6 Figure 7 illustrates an apparatus suitable for large scale manufacture of gel
7 beads, employing the method illustrated in Figure 6. Referring to Figure 7,
8 coolant fluid 50 recirculates from a chiller 52 to an immersion probe 54 immersed
9 in an oil tank 56. Oil is drawn through a filter 58 by a gear pump 60 and
10 delivered to conduit 44 mounted in a tee 62. Gel beads are removed from the
11 emergent stream by a screen 64. Gel solution is mixed in a jacketed glass vessel
12 66 and delivered to venturi tube 40 by a peristaltic pump 68. If desired, the gel
13 beads can be removed from screen 64 to water bath 70.

14
15 The methods and apparatus described herein are generally suitable for making
16 any of the inventive bead compositions described.

17
18 While reference has been made to topical application of compositions containing
19 the novel gel particle delivery systems of the invention, it will be understood that
20 certain such gel delivery systems can, with benefit, be applied to tissues, e.g.
21 wound tissue, and to other environments where the controllable release
22 protection of actives, especially actives dispersed in an excipient, is important
23 and where release of bound actives can be readily initiated.

24 25 **INDUSTRIAL APPLICABILITY**

26 The present invention is particularly suitable for application in the cosmetic
27 industry providing novel consumer cosmetic products, for example, creams, gels
28 and lotions containing gel-complex beads and the gel-complex beads themselves.

29

1 In addition, the ability of the agar complex beads of the invention to deliver
2 labile, biologically active agents to the epidermis makes it possible to
3 contemplate novel anti-actinic cosmetic compositions providing three lines of
4 defense against the ravages of ultra-violet or other solar radiation. The first line
5 of defense is a filtering agent, for example a zinc oxide or titanium dioxide
6 dispersion to screen out ultraviolet or other undesired radiation. The second line
7 of defense is a free-radical scavenger, for example vitamin E, or vitamin C, to
8 repair or prevent damage at the molecular level and the third line of defense is a
9 DNA repair enzyme, as referenced hereinabove to repair damage at the genetic
10 level. These three defensive agents can, according to another aspect of the
11 invention, be provided in a single anti-actinic composition, formulated with
12 excipients as known to those skilled in the art, in amounts known to be effective
13 for the individual defensive agents. The agar-complex gel beads described
14 hereinabove provide a particularly preferred delivery vehicle for the DNA repair
15 enzyme, possibly also for the free-radical scavenger and optionally for the
16 screening agent. While all three agents might be delivered in the same beads, an
17 alternative option is to use different beads for different agents, or combinations
18 of agents, provided that they are substantially uniformly distributed in the end
19 product so that the end-user can generate a suitable mixture of active agents by
20 crushing and spreading a multiplicity of beads on the skin. Equivalents of the
21 individual defensive agents that may be used in such a three-line anti-actinic
22 composition, and other means of delivering them in a cosmetic or therapeutic
23 composition, besides the gel beads described herein, will be apparent to those
24 skilled in the art.

25
26 While some illustrative embodiments of the invention have been described
27 above, it is, of course, understood that various modifications and equivalents of
28 the described embodiments will be apparent to those of ordinary skill in the art.
29 Some equivalents will be readily recognized by those of ordinary skill while

- 1 others may require no more than routine experimentation. Such modifications
- 2 and equivalents are within the spirit and scope of the invention, which is limited
- 3 and defined only by the appended claims.

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